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Development of a Continuous Finishing Chemistry Process for Manufacture of a Phosphorylated Cotton Chronic Wound Dressing

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ABSTRACT: A phosphorylated form of cotton gauze for treatment of chronic wounds was designed to improve the wound dressing's capacity to remove harmful proteases from the wound and facilitate healing. Development of the fabric finishing chemistry of the wound dressing with a process suitable for textile mill production required adapting the stationary finishing chemistry of the cotton phosphorylation from a batch-type pad-dry-cure finishing treatment to a continuous pilot scale finishing process. Issues in optimizing the cotton finishing process took into consideration dressing sterilization, the effect of city water versus de-ionized water, retention of the fabric whiteness index and protease sequestration capacity of the dressing, which is the index of the dressing's efficacy. Three types of sterilization approaches were assessed, including gamma ray, ethylene oxide and steam sterilization to determine the effect of sterilization on the phosphorylated cotton dressing and the subsequent efficacy of the sterilized dressing to remove proteases from the wound. Two phosphorylation reagents were compared for their ability to phosphorylate cotton in a urea-based formulation and yield an active, effective dressing, with a high whiteness index. Phosphorylation with a diammonium phosphate (DAP) : urea formulation generally gave a more effective dressing as an active protease sequestrant, and phosphorylation with sodium hexametaphosphate (SMP) : urea gave a higher whiteness index. Finishing formulations combining the

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two phosphorylating reagents, DAP and SMP : urea, were assessed to improve both whiteness and efficacy. However, sterilization of DAP treated cotton with ethylene oxide eradicated activity through apparent masking of the cellulose phosphate hydroxyls. Side reactions that may occur during ethylene oxide treatment were discussed as the possible origin of the phosphate hydroxyl masking. On the other hand, sterilization with gamma irradiation produced significant yellowing of the dressing. A SMP : urea (16 : 30) formulation was employed in the continuous process finishing treatment, and found to be most optimal for whiteness, efficacy and ease of sterilization, when adapted to industrial scale production of the cotton chronic wound dressing.

KEY WORDS: chronic wound dressing, elastase reduction, phosphorylated cotton finishing, textile sterilization, rinse water effects.

INTRODUCTION

WOVEN AND NONWOVEN gauze has been manufactured and utilized for the last two centuries in the care of both acute and chronic wounds [1]. Cotton and cellulose-based wound dressings are still a standard in hospital and nursing home wound care, and in recent years fiber, yarn and nonwoven modifications have improved its quality and versatility in medical applications [2–5].

Chronic wounds have become a worldwide health problem [6]. For the 5 million Americans suffering from chronic open wounds it is estimated that $5–7 billion per year is spent, and this is increasing at an annual rate of 10% [7]. Chronic wounds occur as a result of incomplete healing that occurs when a wound becomes arrested in the inflammatory stage of healing [8]. An over exuberant supply of neutrophils occurs in the inflammatory stage of wound healing [9]. Since neutrophils possess an armament of biochemical weaponry that is used against bacteria, the release of destructive proteases from excess neutrophils becomes a threat to healing when a high concentration occupies the wound environment [10]. In this regard, the protease human neutrophil elastase found in high concentration in the chronic wound creates considerable protein destruction and prevents the wound from healing [11]. The design of wound dressings that selectively sequester proteases from the chronic wound has been based on the concept that molecular features of the protease including protein size, charge, and active site mechanism may be used to tailor the molecular design of the dressing material used to capture it [5,11–15]. In our initial proof-of-concept experiments we showed how elastase substrate peptides could be tethered to cotton cellulose and used successfully to capture the protease in solution [13]. Commercial development of a mechanism-based wound dressing [16] that would offer an economic, highly effective product

prompted that the product be based on a mode of action related to the ionic binding of cationic serine proteases and matrix metalloproteases to the dressing. Thus, an approach was adopted employing phosphorylated cellulose utilizing a set of finishing chemistries for cotton modification that would be compatible with current cotton textile processing technology.

MATERIALS AND METHODS

Dressing Treatments

Cotton gauze (36 in. wide folded to 4 ply (8 in.)) with a 24/20 thread count was supplied by DeRoyal Textiles, Camden SC. Two different phosphorylation treatments of cotton wound dressings were performed using a phosphorylating reagent and urea. Formulations of all padding solutions were prepared as % by weight (w/w). Urea was dissolved in ~80% of the calculated formulation water and warmed to room temperature. Then the phosphate was added slowly, followed by wetting agent, after which the final formulation weight adjustment was made with water. Reagents used for these treatments include sodium hexametaphosphate (SMP) (CAS 10124-56-8) EM Chemicals or sodium polyphosphate (CAS 68915-31) Astaris Inc., diammonium phosphate (DAP) (CAS 7783-28-0) Astaris Inc., and urea (CAS 57-13-6) from Highlands Chemical Corp., Highlands NC. For laboratory scale noncontinuous processing, gauze padding was done on a Mathis Padder Type HVF; pressure adjusted to give 100% wet pickup (~1.2 bar). The gauzes were padded with either a SMP (sodium polyphosphate can be used interchangeably): urea (16% : 30%, wt%: wt%) solution or a DAP: urea (10% : 30%, wt%: wt%) solution. IGEPAL-CA630 (octylphenol ethoxylated CAS 9002-93-1, Rhodia Inc., Cranbury NJ) was used as wetting agent and added as 0.1% of padding solution. Individual swatches were placed on pin frames and dried at 90°C for 3 minutes in a Mathis Labdryer Type LTE (pop-out type oven). The cotton fabrics were cured in a second oven at the selected temperatures for the desired time. The curing temperatures and times were 160–175°C for 3–7 min for SMP and 140–160°C for 2–5 min for DAP. Individual swatches were rinsed 3 times in deionized water and air dried or dried in a pop-out oven.

Continuous Finishing Process

Pilot Scale Processing

The pilot scale continuous finishing and curing process for phosphorylation of the woven cotton gauze was implemented on a pad-dry-curing

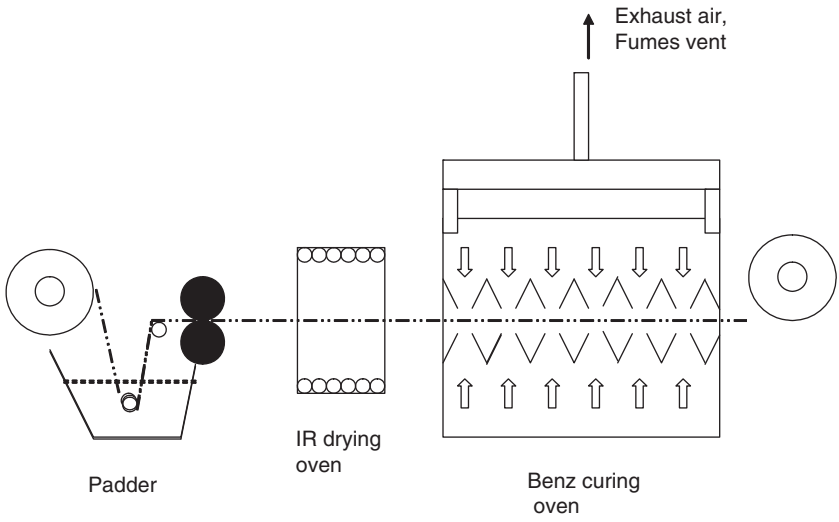

FIGURE 1. Design configuration of the continuous finishing process as described in the Materials and Methods section.

equipment configuration as shown in Figure 1. Continuous application of 30% urea : 16% sodium polyphospate : 0.1% IGPEAL was performed on a Mathis Padder Type HVF at a padder roller pressure of 1.2 bar with woven cotton gauze prepared by DeRoyal Textile Industries, Camden SC. For continuous treatments, roll gauze proceeded from textile padder through a Mathis IR dryer into an Ernst Benz KTF oven at selected temperature with speed adjusted to achieve the desired dry/cure times. Fabric thermal conditions in the Benz oven were determined through a temperature profile of a cotton fabric placed on a conveyor belt and run through the oven (Figure 2). Set point temperatures required for curing were attained in the oven interior 12 in from the fabric entrance point as shown in Figure 2.

Industrial Scale Processing

The industrial pad-dry-cure process for treatment of the cotton gauze was configured similar to the pilot scale process. The industrial process employed an industrial scale padder, dryer oven and curing oven housed at DeBusk Knitting (Tazwell TN). The padding rollers were set at a pressure of 7 psi, which gave a wet pickup of 159%. The drying and curing ovens could accommodate 83 ft of cotton gauze. Oven temperature was monitored with four thermocouple probes place in varying regions of the oven.

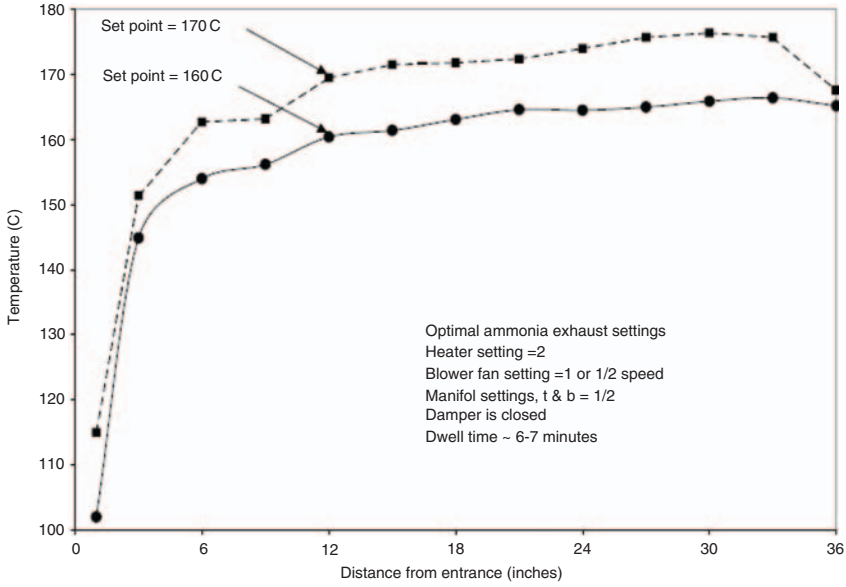

FIGURE 2. Temperature profile of oven used for continuous process finishing. Temperatures were measured on dried fabric running through the oven, using an elongated probe with a type-T thermocouple inserted just over the fabric at defined distances from the oven inlet. Temperature at each location was monitored with an Oakton digital temperature meter, Model 8536-25, Input ISA-T (Cole-Parmer Instruments, Chicago IL). The graph compares the profile at two temperature settings, both at heater setting 2 and with damper fully closed. Closing damper was necessary to eliminate smoke release into the room.

Following the curing, the cotton gauze was rinsed by immersion in deionized water contained in three separate water baths placed on line after the curing oven.

Whiteness Index

CIE whiteness index was measured according to AATCC Test Method 110-1989 using a Milton Roy Color Mate Color Analyzer (Milton Roy Company, USA).

Elastase Assay

Treated and untreated gauze samples (0.2 g) were submerged in 1 mL of 4% bovine serum albumin (BSA) in buffer (pH 7.6 buffer composed of 0.1M sodium phosphate, 0.5 M NaCl) containing 84 m unit/mL of human neutrophil elastase. Samples were allowed to incubate for 1 hour at room

temperature, after which they were removed and placed in a 5 mL syringe and pressed to drain unbound protein, buffer and enzyme. The unbound elastase fractions were combined and assayed for elastase activity. Enzyme assays of the solutions containing unbound human neutrophil elastase were conducted in pH 7.6 buffer described above and subjected to spectrophotometric measurement of the release of p-nitroaniline at 410 nm from the enzymatic hydrolysis of N-Methoxysuccinyl-Ala-Ala-Pro-Val-p-nitroanilide (Sigma) [16]. The spectrophotometric kinetic assays were performed in a Bio-Rad Microplate Reader (Hercules, CA) with a 96-well format (14).

RESULTS

Industrial development of the phosphorylated cotton gauze, as a chronic wound dressing, prompted consideration of both product and process issues effecting the appearance, quality, and efficacy of the dressing. The goal of the wound dressing development was to maintain protease sequestrant efficacy of the chronic wound dressing, while retaining desirable properties including fabric whiteness, and uniform finishing treatment of the woven fabric. Protease sequestrant efficacy is defined as the ability of the modified dressing to lower human neutrophil elastase activity in the wound relative to untreated cotton dressing. Thus, the sequestrant efficacy of the dressing is a result of the dressing capturing proteases and removing them from the wound environment. Issues that arose in transferring the process finishing chemistry for the dressing modification from a stationary finishing process to a continuous process included the effect of fabric curing, sterilization, and water quality on the dressing's whiteness index and protease sequestrant efficacy. The continuous finishing process was piloted on a system configured at Southern Regional Research Center where a padder, IR drying oven, and curing oven were configured into a continuous processing line as diagrammed in Figure 1. To develop appropriate oven conditions for a continuous finishing process, dynamic oven conditions were assessed using a Benz oven. Dwell times in the Benz oven within a 160–170°C temperature range were 6–7 minutes (Figure 2).

The phosphorylation finishing chemistry employed was based on the high-temperature reaction of one of two reagents (SMP or DAP) in a formulation employing urea (typically applied as 30% of the total formulation). Urea promotes the biphasic reaction between the cellulose and the phosphorylating reagent (see reaction schematic shown in Figure 3), and the release of ammonia from urea decomposition during the reaction required engineering exhaustion of ammonia from the curing oven (see conditions stated in Figure 2 inset). The effect of the two different finishes

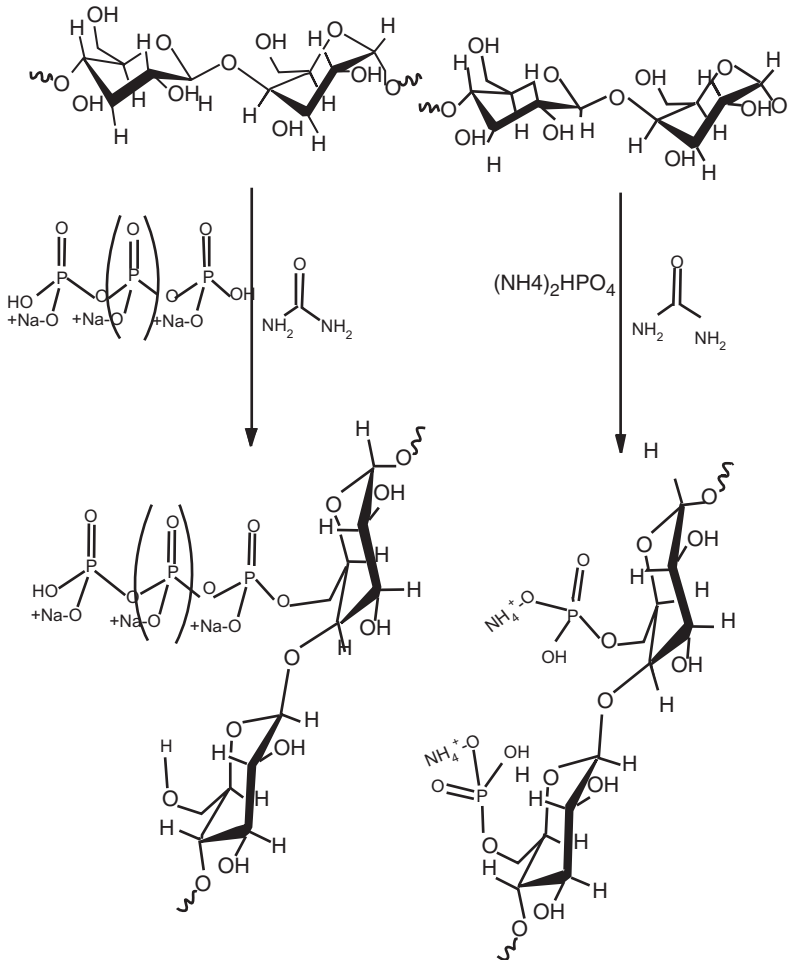

FIGURE 3. Reaction pathways for phosphorylation of cellulose with SMP and DAP. Both reactions are run in the presence of urea as outlined in Materials and Methods.

on the protease sequestrant efficacy of the phosphorylated cotton wound dressing has been previously reported [16]. The typical temperature range for assessing the curing conditions with SMP was 160–175°C.

Sodium hexametaphosphate, which is a polymeric phosphate salt, can be cured on cotton in the presence of urea at a high temperature (160–170°C) without yellowing of the fabric when compared with DAP (Figure 4(b) and (e)). On the other hand, the DAP: urea finishing and curing gave higher add-ons (Figure 4(f) and (c)), but even curing at lower temperature with these formulations gave rise to some slight discoloration of the cotton fiber

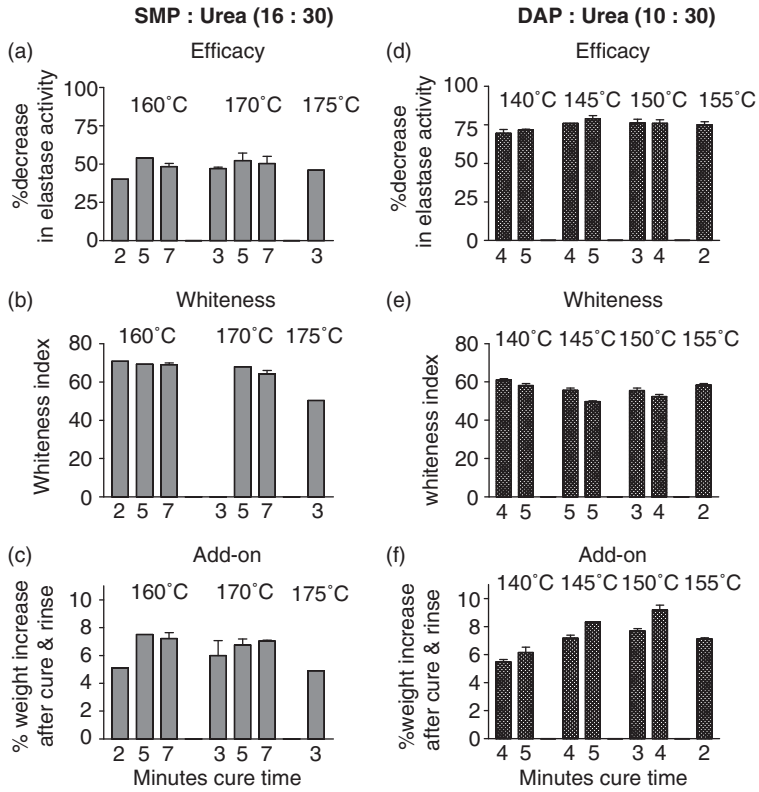

FIGURE 4. A comparison of the effect of phosphorylating formulations and curing conditions (temperature and time) on efficacy (% elastase activity decrease compared to untreated control), whiteness and add-on. Solid bars (a, b, c) – treated with SMP : urea (16 : 30); crosshatched bars (d, e, f) – treated with DAP : urea (10 : 30). Fabrics were treated in a lab scale batch process.

as seen by the lower whiteness index in Figure 4(e). Assessment of the phosphorylated cotton gauze's protease-lowering efficacy, when cured under stationary oven conditions, showed that DAP : urea at a percent ratio by weight of 30 : 10 (urea : PO4) gave higher protease-lowering activity when compared with SMP as the phosphorylating reagent (Figure 4(a) and (d)). This result of higher add-ons correlating with better protease sequestrant efficacy is consistent with previous work, where the increase in cellulose phosphorylation was correlated to an increase in protease sequestrant efficacy [16]. Thus, to improve whiteness and retain efficacy a series of formulations containing a combination of DAP and SMP were cured on the cotton gauze. The effect of the combined formulation of DAP and SMP on efficacy and whiteness are shown in Figure 5. The effect of incorporating

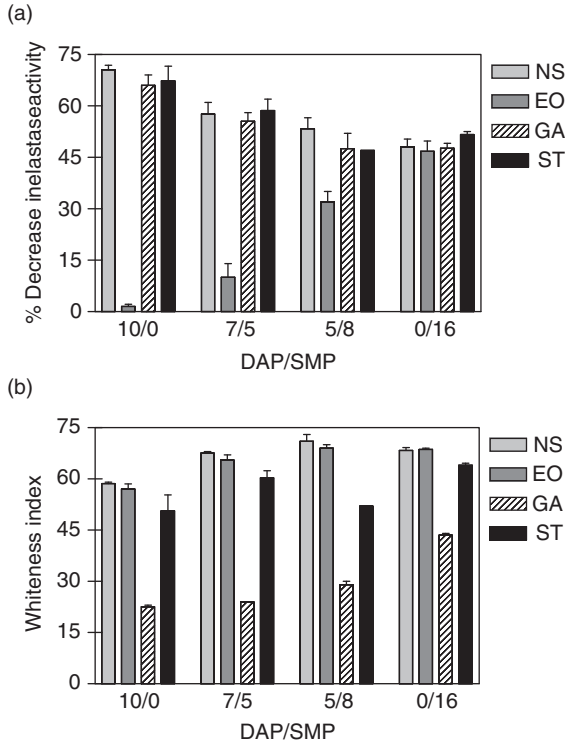

FIGURE 5. Effect of three methods of sterilization on (a) efficacy (% elastase activity decrease compared to untreated control) and (b) whiteness of cotton gauze treated with urea and various combinations of DAP and SMP. NS = nonsterile; EO = ethylene oxide; GA = gamma irradiation; ST = steam.

SMP improved whiteness (Figure 5(b)) but the higher protease sequestrant efficacy observed with DAP formulations was not retained with the inclusion of SMP (Figure 5(a)).

It was deemed that the successful commercialization of the cotton wound dressing was partially dependent on a reproducible cotton fabric product of acceptable whiteness. A series of phosphorylated cotton wound dressings, which had been treated under stationary finishing and curing conditions with either the SMP or DAP treatments were visually assessed for whiteness by DeRoyal Textiles, a major manufacturer of cotton gauze, according to standards of whiteness for cotton wound dressing products. The manufacturer's visual assessment of the dressing's whiteness was employed to determine a minimum acceptable whiteness index of 60 (based on measurements taken with a Milton Roy Colormate Instrument). Figure 4(b) and (e) contrasts the fabric whiteness for both curing treatments. The SMP

treatment gave a better whiteness index than the DAP treatment. However, the DAP treatments were found to be acceptable to marginally acceptable for most of the samples tested, and they were generally more effective as a protease sequestrant (Figure 4(a) and (d)).

The effect of three different types of sterilization on efficacy and whiteness is also shown in Figure 5. The type of sterilization utilized was found to play a major role toward choosing the appropriate process development of the phosphorylated cotton dressing. The phosphorylated cotton wound dressing samples were assessed for the effect of ethylene oxide sterilization conditions at DeRoyal Textiles. The relationship of cotton dressing activity before and after sterilization is shown in Figure 5(a). It was found that ethylene oxide sterilization deleted virtually all of the observable protease sequestrant activity of the DAP treated cotton. The effect of ethylene oxide treatment on wound dressing activity is thought to occur through modification of the phosphorylated cotton with ethylene oxide. The mechanism of phosphate hydroxyl modification is not well understood; however, the loss of dressing activity found when ethylene oxide is used to sterilize DAP-treated cotton is thought to be a result of one of the putative reactions outlined in Figure 6. Formation of the phosphate ester or enol removes the anionic charge from phosphorylated cellulose and thus the ability of the dressing to bind the cationic serine proteases and remove them from the wound environment. The reaction of phosphorylated cotton with ethylene oxide occurs with DAP and not SMP cured cotton. Thus the release of free ammonia may account for part of the driving force of the reaction due to the ammonium counterions on the phosphorylated cellulose. A comparison of FTIR spectra (Figure 7) of ethylene oxide-sterilized and steam-sterilized dressings revealed two areas of the spectra that showed differences and serve as a corollary to the observed loss of protease sequestrant dressing activity. The spectrum of steam sterilized phosphorylated cotton demonstrates a broad and significantly increased band of absorption centered at $1000\,cm^{-1}$ when compared with untreated cotton. This increase in absorption can be ascribed to the P(O)-OH (single hydroxyl), which gives a strong stretching frequency signal centered near $1000\,cm^{-1}$ [17]. On the other hand, the spectrum of ethylene oxide sterilized cotton demonstrates a significant decrease in the intensity of this IR band centered at $1000\,cm^{-1}$. Of interest as well is the increased absorption and distinguishing bands observable at $730–665\,cm^{-1}$, which can be correlated to a cis double bond (Figure 6). The IR bands observed in this region of the spectrum suggest a phosphoenol ethylene analog of cellulose may account for masking of the hydroxyls, as shown in Figure 6. Bands belonging to the stretching frequencies of the cellulose structure itself obscure areas of the spectrum that might be directly correlated with a phosphate ester (Figure 6). In addition, the dressings were subject to

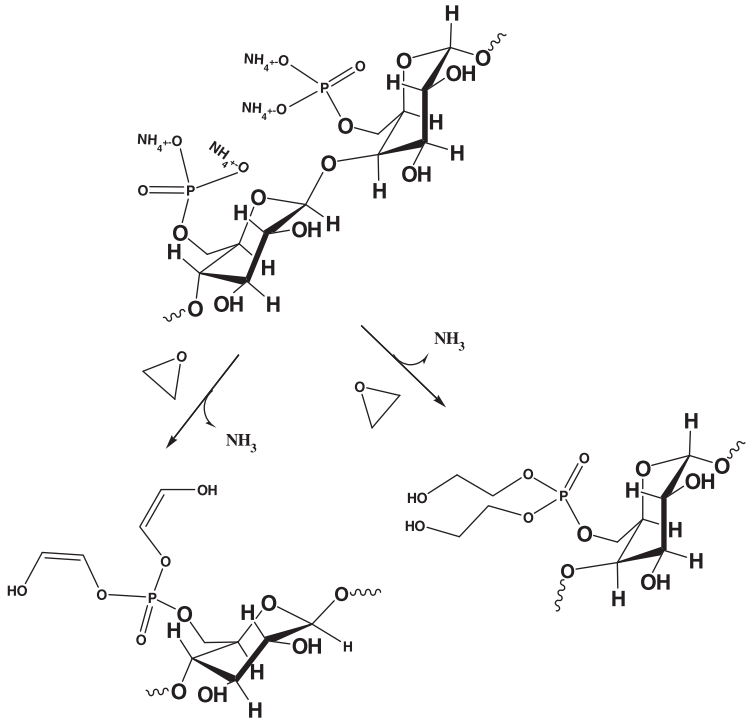

FIGURE 6. Two independent reactions of ethylene oxide with phosphorylated cellulose, which may account for loss in protease sequestrant activity by masking the anionic phosphoryl hydroxyls. Shown here as putatively separate reactions with release of ammonia as the driving force of the reaction mechanism for product formation of a phosphoester or phosphoenol adduct of cellulose.

gamma irradiation and steam sterilization. Gamma irradiation was found to produce significant yellowing (Figure 5(b)) of the phosphorylated cotton dressing even though protease sequestrant activity was essentially retained (Figure 5(a)). On the other hand steam sterilization gave comparable efficacy (Figure 5(a)) with only a slight decrease in whiteness (Figure 5(b)) when contrasted with similar nonsterile treatments. However, the manufacturer chose not to employ steam sterilization treatment. Thus, process formulations that favored ethylene oxide sterilization were chosen.

It was also found in the course of developing the phosphorylated cotton gauze that rinsing with city water decreased the elastase sequestrant efficacy of treated fabrics. This effect was found to be variable and though it did not occur all of the time, when it did occur the desired activity could be restored with ammonium chloride. It previously has been shown that calcium deactivates the flame retardancy of phosphorylated cotton [18], and can

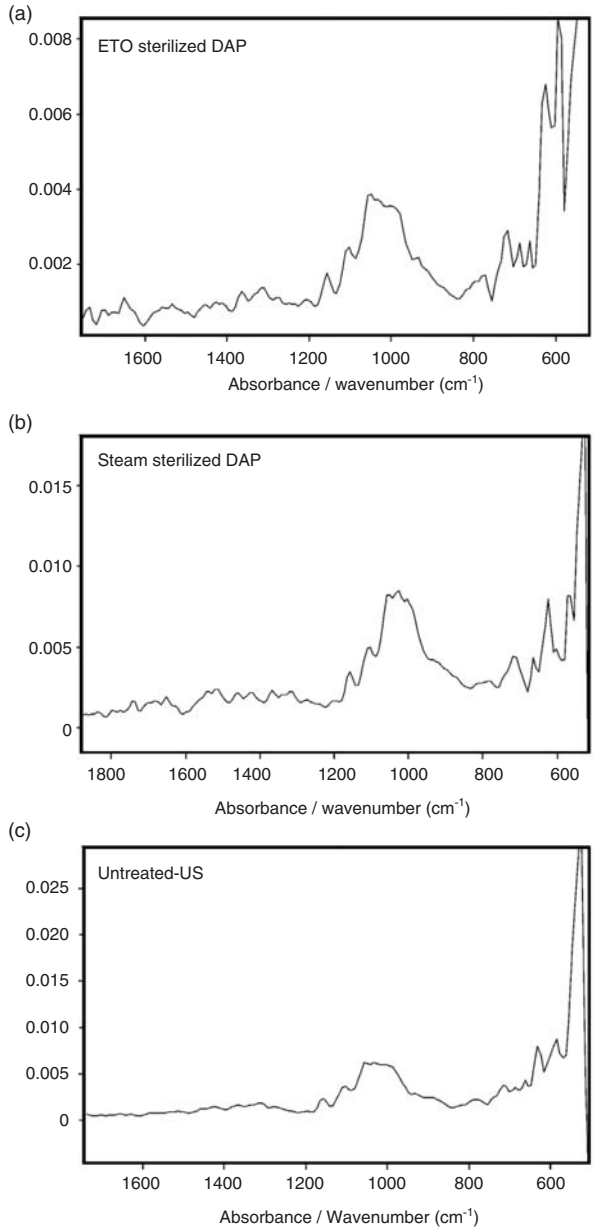

FIGURE 7. Comparison of Fourier Transform Infra-red spectra of sterilized phosphorylated cotton, (a) IR spectrum of steam sterilized dressing treated with urea : DAP (30 : 10), (b) IR spectrum of ethylene oxide sterilized dressing treated with urea : DAP (30 : 10), (c) IR spectrum of untreated sterilized dressing.

Table 1. Effect of rinse water conductivity on efficacy.

	Conductivity ppm[a] (std dev)				Cure[b] temperature (°C)	Efficacy[c] average (std dev)
	Initial	1st rinse	2nd rinse	3rd rinse		
Deionized water	0	1840 (195)	358 (88)	61 (17)	160	40.8 (30)
					170	39.6 (38)
					177	33.9 (31)
Municipal water	234	1899 (149)	458 (81)	246 (6)	160	34.8 (41)
					170	34.0 (5.0)
					177	29.1 (8.4)

[a]Conductivity measured as parts per million (ppm) total dissolved solids.
[b]Cure times: 6–9 minutes @ 160°C; 4–8 minutes @170°C; 2–4 minutes @177°C.
[C]Efficacy = % decrease of elastase activity relative to untreated fabric.

block the effectiveness of the FR finish after laundering. Municipal water often contains calcium carbonate at levels of 100 ppm and is most likely the source of the inactivation of phosphorylated cotton. Interestingly, some cities use SMP to precipitate calcium from municipal water during purification treatments. Table 1 compares deionized water and municipal water rinses for their effect on protease sequestrant efficacy. Using municipal water taken from the manufacturer's location (conductivity of 234) in the post-curing rinses was found to result in less protease sequestrant efficacy than using deionized water (Table 1). It was also found that three separate deionized water rinses were needed to lower the conductivity of the water within a range that was commensurate with optimal efficacy.

The formulation chosen for pilot development of the cotton chronic wound dressing was SMP : urea (16 : 30). As diagrammed in Figure 1, the dressing was pad-dry-cured in a continuous process by applying this formulation to cotton gauze. The resulting effect of curing temperature on protease sequestrant capacity and whiteness are shown in Figure 8. The temperature range and oven dwell-time were assessed as a function of the rate of curing in the continuous process. In this regard it was found that a slower processing time of curing coupled with lower temperatures and thus longer oven dwell times promoted better protease sequestrant efficacy in the cotton gauze (Figure 8). However, although there is a slight improvement in protease sequestrant activity with increased time at lower temperatures the effect of curing conditions within the curing time and temperature range assessed was essentially equal. As seen in Figure 9, in a similar manner industrial processing of the cotton gauze resulted in a very similar profile, where the dressing was observed to reduce protease activity by 40% when compared with untreated controls.

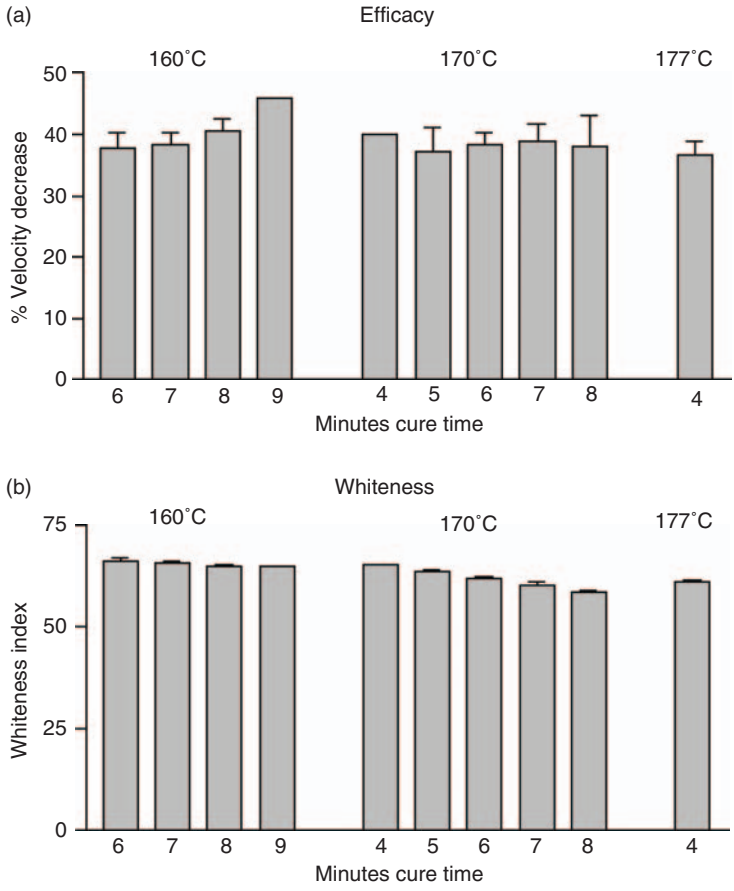

FIGURE 8. Effect of cure time and temperature on (a) protease sequestration efficacy and (b) fabric whiteness of gauzes padded with 30% urea : 16% SMP in a pilot plant scale continuous process.

CONCLUSIONS

The development of an effective economical protease sequestrant dressing for chronic wound treatment addresses an unmet need of pressure ulcer and chronic wound patients in the medical textile and health care sectors. The principle concerns required to transfer the phosphorylation of cotton dressings from a laboratory scale process to an industrial scale process were curing rates, sterilization and water conductivity. Thus the advantage of assessing two types of phosphorylation reagents was realized in the eventual outcome to choose the best formulation given the manufacturers

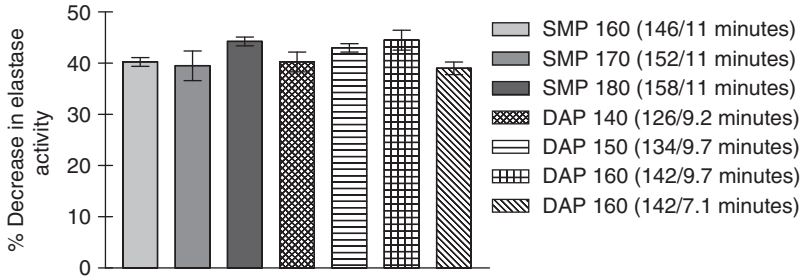

FIGURE 9. Comparison of protease sequestration efficacy of two formulations applied on commercial pad-dry-cure equipment. Legend indicates phosphorylation reagent, sodium hexametaphosphate, SMP, or diammonium phosphate, DAP, and nominal oven setting; in parentheses (actual average oven temperature ±20°C /actual dwell time).

requirements and the clinical properties of the dressing. The development of a pilot scale process early on in the development of the dressing proved beneficial in scaling up the process to a manufacturing scale. The outcome of this work was realized in a safe, reproducible process for production of a cotton-based chronic wound dressing which gained FDA approval http://www.fda.gov/cdrh/510K/sumjul06.html 501 K number: K061060 and is currently undergoing commercialization.

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BIOGRAPHY

Dr J. Vincent Edwards has worked for 10 years combining and adapting the concepts of bioactive molecules with traditional textile chemistry approaches to create new value-added biomedical cotton products for industrial licensing. He has worked in numerous research positions within industry and government in the fields of medicinal, peptide and gene delivery chemistry. Prior to his current position with the USDA, he was in the field of nonviral gene therapy research between 1994 and 1997 at GeneMedicine, Inc., Woodlands, TX., where he lead efforts to develop peptide-based gene delivery systems for diseases of the lung, liver, and solid tumors. As a senior research scientist in the pharmaceutical industry at Marion Merrill Dow, Cincinnati OH between 1988 and 1994, he developed compounds for product development including anti-tumor growth factors, peptide lung surfactants, anti-viral conjugates of the CD4 receptor of HIV-1 and medicinal chemistry optimization of peptide combinatorial library leads. His Ph.D. dissertation research in the field of opioid peptide synthesis and structure-function studies lead to the development of a highly potent opioid peptide demonstrating great potential in both receptor studies and oral activity. Dr Edwards research and development work has been documented in 9 patents, 60 co-authored publications, and 2 edited books.